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Original Article

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Prognostic utility of B-type natriuretic peptides in patients with heart failure and renal dysfunction

Bård Waldum[1,2], Viera Stubnova[2], Arne S. Westheim[3], Torbjørn Omland[1,4], Morten Grundtvig[5] and Ingrid Os[1,2]

[1]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [2]Department of Nephrology, Oslo University Hospital, Ullevål, Oslo, Norway, [3]Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway, [4]Department of Cardiology, Akershus University Hospital, Lørenskog, Norway and [5]Department of Medicine, Innlandet Hospital Trust, Lillehammer, Norway

Correspondence and offprint requests to: Bård Waldum; E-mail: bard.waldum@medisin.uio.no

Abstract

Background. Renal dysfunction is considered a confounding variable in the interpretation of B-type natriuretic peptides (BNPs) and their amino-terminal fragments (NT-ProBNP) in patients with heart failure (HF). Our aim was to investigate the prognostic utility of BNPs and NT-proBNP in HF outpatients with renal dysfunction, and compare the prognostic significance of the corresponding BNP/NT-ProBNP levels in patients with and without renal dysfunction.

Methods. A total of 2076 patients from 13 HF clinics in the Norwegian Heart Failure Registry were investigated. The BNP/NT-ProBNP levels were categorized centre-wise into four groups using the quartile limits found in patients with preserved renal function. Patients with renal dysfunction, i.e. glomerular filtration rate (GFR) $\leq$60 mL/min/1.73 m^2, were then assigned to BNP groups 1–4 centre-wise according to their level of natriuretic peptides.

Results. Renal dysfunction was present in 37.5% of the patients, of whom the majority (59.1%) had levels of natriuretic peptide in the highest BNP group. Patients with renal dysfunction and BNP levels in the lower three BNP groups had similar 2-year survival as patients without renal dysfunction and comparable BNP levels [crude hazard ratio (HR) 1.25, 95% CI 0.82–1.89, P = 0.302, multiple adjusted HR 0.85, 95% CI 0.54–1.33, P = 0.457]. Beyond 2 years of follow-up, renal dysfunction predicted all-cause mortality irrespective of the level of natriuretic peptides at the start of follow-up.

Conclusion. In HF outpatients, the BNP/NT-ProBNP level predicted 2-year mortality irrespective of renal function and provided important prognostic information on patients with renal dysfunction.

Keywords: B-type natriuretic peptides; heart failure; prognostic marker; renal dysfunction

Introduction

The patient B-type natriuretic peptide (BNP) level measured either as the bioactive hormone BNP or as the inactive amino-terminal fragment (NT-proBNP) is established as a sensitive diagnostic marker of heart failure (HF), and elevated levels are strong independent predictors of mortality in HF patients [1–4]. BNP and NT-proBNP are assumed to provide similar information about cardiac production of natriuretic peptides [2, 3].

Renal dysfunction is regarded as a confounding factor when evaluating the level of natriuretic peptides in HF patients. The kidneys are considered important in the clearance of both BNP and NT-proBNP, and the levels are often elevated in patients with renal dysfunction even in the absence of clinically overt HF [4]. However, the contribution of the kidneys in the removal of the natriuretic peptides is controversial [5–7]. Chronic kidney disease (CKD) is associated with cardiovascular disease [8, 9], and BNP elevation in asymptomatic patients with CKD has been shown to reflect ischaemic heart disease (IHD) and left ventricular hypertrophy [10, 11]. Renal dysfunction is common in HF patients [12–14], and the uncertainty in the interpretation of the natriuretic peptides in patients with renal dysfunction may limit the use in clinical practice.

Our aim was to investigate the prognostic utility of BNP and NT-proBNP in patients with chronic HF and renal dysfunction by comparing the prognostic significance of the corresponding BNP/NT-ProBNP levels in patients with and without renal dysfunction.

Materials and Methods

The Norwegian Heart Failure Registry

The Norwegian Heart Failure Registry was initiated in October 2000 with the intent to collect data on outpatients with HF attending office visits in HF clinics in Norway

[15]. By March 2011, the number of participating clinics counted 24, situated in all regions in Norway; at that time 6482 patients were included. Cardiologists in cooperation with specially trained nurses run the HF outpatient clinics. All patients with HF of any aetiology, New York Heart Association (NYHA) function classes I–IV, diagnosed clinically according to the guidelines from the European Society of Cardiology, were enrolled consecutively in the HF clinics. At the first visit, medical history, physical examination, echocardiography, laboratory results and the medical management of HF were registered. After adjustment of medical therapy and undergoing an educational programme, Visit 2 was recorded. If required, additional clinical visits could be scheduled to ensure optimization of therapy before Visit 2. Finally, Visit 3 was planned to occur 6 months after Visit 2. Mortality data were retrieved from the Norwegian death registry kept by Statistics Norway. The current database was updated with respect to mortality data by March 2011. All participants provided written informed consent prior to inclusion in the database. Only unidentifiable data were entered in the database. Permission for this analysis was granted from the National Data Inspectorate and the Regional Committee of Medical and Health Research Ethics.

Construction of BNP groups

The analyses of BNP and NT-proBNP were performed at various hospitals using different assays. Natriuretic peptides, analysed using various methods, are not necessarily comparable even when analysing the same peptide [16]. In order to take into account different reference values and methods, patients were allocated to BNP groups centre-wise to be able to analyse the prognostic information of higher and lower levels of natriuretic peptides across centres. The BNP groups were defined by quartile limits in patients without renal dysfunction, i.e. estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2. Patients with an eGFR of ≤60 mL/min/1.73 m^2 were centre-wise then assigned to BNP groups 1–4 according to their level of natriuretic peptides (Figure 1). By using this method to compare the levels of natriuretic peptides across centres, we assumed that the HF populations at each centre were comparable and that allocation to the BNP group was independent of the assay used if BNP or NT-ProBNP was the analysed peptide. Centres included had to have a sufficient number of patients, arbitrarily set to 40 or more, analysed with the same assay. Patients from 13 outpatient clinics were included in the analyses. The patients were stratified according to their BNP or NT-proBNP level measured at the last attended visit. At this point, the medical treatment should be optimized in all patients. The cut-off levels for BNP groups varied among the centres as different methods were utilized. The average NT-proBNP levels which were used to define the BNP groups at the different centres were for Group 1, <495 pg/mL; Group 2, 495–1006 pg/mL; Group 3, 1006–2180 pg/mL and Group 4, >2180 pg/mL, while for BNP < 91 pg/mL, these were 91–204 pg/mL, 204–504 pg/mL and >504 pg/mL in the four groups, respectively. Assays of NT-ProBNP were used in the majority of patients (1399 patients, 67.4%) compared with assays of BNP.

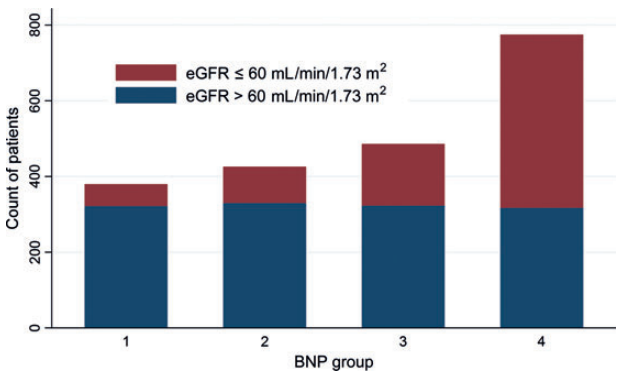

Fig. 1. Distribution of 2076 outpatients with HF in the four BNP groups, classified by renal function. BNP groups were defined at each participating centre by quartile limits in patients with preserved renal function. Patients with renal dysfunction were then allocated to BNP groups centre-wise due to their level of natriuretic peptides. Bars represent the cumulative number of patients in each BNP group. Patients with preserved renal function are presented in blue and patients with renal dysfunction are presented in red. BNP = B-type natriuretic peptide, eGFR = estimated glomerular filtration rate.

Definitions

Renal function assessed as eGFR was estimated based on the simplified Modification of Diet in Renal Disease prediction equation. Renal dysfunction was defined as eGFR ≤60 mL/min/1.73 m^2. Lack of information on the degrees of albuminuria and other signs of renal damage made evaluation of the full spectrum of CKD impossible.

A high proportion of the population was at baseline already treated with diuretics, drugs blocking the renin–angiotensin-aldosterone system and β-blockers. To differentiate between treatment intensity, the patients were categorized into three groups of treatment intensity, i.e. not on actual drug, low dose defined as daily dose ≤ median value and high dose defined as daily doses > median values. Daily doses of loop diuretics were calculated in furosemide equivalents (bumetanide 1 mg = furosemide 40 mg). Doses of angiotensin-converting enzyme inhibitors (ACEi) were calculated as enalapril equivalents per day (captopril 5 mg = ramipril 0.5 mg = lisinopril 1 mg = enalapril 1 mg). ACEi were more frequently used than angiotensin receptor blockers (ARBs), ARB daily doses were not converted to ACEi daily dose. Daily dose of β-blockers was calculated as metoprolol equivalents (bisoprolol 1 mg = carvedilol 5 mg = atenolol 10 mg = metoprolol 20 mg).

Vascular disease was defined as previous stroke and/or peripheral arterial disease. The diagnosis of IHD as the cause of HF was based on clinical evaluation at the time of inclusion.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or median with the interquartile range (IQR) for non-normally distributed data. Categorical data were presented as percentages. ANOVA analyses were used to check for trends of continuous data with increasing BNP groups. For the same purpose, chi-square tests were utilized to compare categorical data.

A logistic regression model was used to investigate the differences between patients who were included in the study compared with the rest of the HF registry who did not have valid BNP registrations. The variables achieving

$P < 0.10$ on univariate analyses were included in the multivariate model.

Kaplan–Meier survival curves were calculated and Log-rank statistics were used to investigate univariate difference in all-cause survival during the observation period, between patient groups. Nelson–Aalen plots were constructed to describe the hazard by time in patients with renal dysfunction and BNP groups 1–3.

Cox regression analyses were used to determine the association of categories of the BNP group and renal function with all-cause mortality. Patients with preserved renal function (eGFR > 60 mL/min/1.73 m^2) and relatively low BNP levels (BNP groups 1–3) were set as reference category. To fulfil the assumption of proportional hazards, separate Cox analyses on 2-year all-cause mortality and all-cause mortality beyond 2 years were performed. Univariate hazard ratios (HRs) were presented as well as HR adjusted for age and gender and a multivariate adjusted Cox model. Due to the limited number of events in each subgroup, the number of variables in the multivariate model had to be restricted. A multivariate Cox regression analysis with outcome all-cause mortality using the entire study population was performed to identify factors to correct for in the subgroup analyses. Backward selection with a cut-off P-value of 0.10 was used for variable selection. Initially, 21 variables were entered. Age, IHD, atrial fibrillation, history of hypertension and NYHA class in addition to GFR and BNP group were significant predictors of all-cause mortality in the entire population and were entered in the further multivariate cox analyses.

For each Cox model the proportional hazard assumption was checked and found to be adequately met [17]. Interaction analyses by product terms were checked with respect to gender, ejection fraction and type of analysis for natriuretic peptides, i.e. BNP or NT-ProBNP. The level of significance was set at 0.05. Analyses were performed using IBM SPSS statistical software (IBM SPSS, Inc., Chicago, IL, v.19.0). Kaplan–Meier and Nelson–Aalen curves were computed in STATA version 11.0.

Results

A total of 2076 patients in the Norwegian Heart Failure Registry were allocated to a BNP group and included in the analyses. The BNP groups were defined by the quartile limits in patients with preserved renal function at each centre, i.e. Group 1 had the lowest levels of BNP/NT-proBNP and Group 4 had the highest. The included patients constituted 33.3% of the total population in the registry. Patient characteristics of the study population stratified into the four BNP groups are presented in Table 1. A total of 775 patients (37.5%) had renal dysfunction, i.e. eGFR < 60 mL/min/1.73 m^2, and no patients on dialysis were included. The majority of patients with renal dysfunction (458 patients, 59.1%) had BNP values in the highest BNP group, i.e. average of all centres NT-proBNP > 2180 pg/mL or BNP > 504 pg/mL. The distribution of patients in the different BNP groups stratified by renal dysfunction is shown in Figure 1. The median follow-up from the last visit was 30 months (IQR 15–48 months). The median eGFR in patients with renal dysfunction was 46.6 mL/min (IQR 37.9–53.6 mL/min).

The 317 patients (40.1%) with renal dysfunction and BNP levels within the lower three BNP groups had a similar prognosis at 3 years of follow-up (log-rank $P = 0.195$). However, patients with renal dysfunction within the highest BNP group had a considerably worse prognosis than the patients within the lower three BNP groups with 3-year survival 57% compared with 85% (Figure 2, log-rank $P < 0.001$).

The prognostic significance of comparable BNP values in patients with and without renal dysfunction was analysed. Patients with an eGFR $\leq$60 mL/min/1.73 m^2 and BNP levels in the lower three BNP groups had overall a worse prognosis than patients with an eGFR >60 mL/min/1.73 m^2 in the same BNP groups (Figure 3a). Three-year survival was 81% compared with 86% (log-rank $P < 0.022$). However, the increased hazard was not proportional, the hazard of all-cause mortality among patients with renal dysfunction and within the lower three BNP groups increased exponentially by time (Figure 3b). Analyses of 2-year survival revealed that the patients with renal dysfunction had no additional risk of all-cause mortality, given that their BNP levels were in the lower three BNP groups (crude HR 1.25, 95% CI 0.82–1.89, $P = 0.302$, multiple adjusted HR 0.85, 95% CI 0.54–1.33, $P = 0.467$, Table 2). Beyond 2 years of follow-up, the risk of all-cause mortality was significantly higher in the same patients (crude HR 2.66, 95% CI 1.81–3.90, $P < 0.001$, multiple adjusted HR 1.97, 95% CI 1.27–3.07, $P = 0.003$, Table 2).

There were no interactions with gender or ejection fraction in the Cox models. No interaction was found regarding the type of analyses for natriuretic peptides used, i.e. BNP or NT-ProBNP. Entering treatment centre as a categorical variable into the different multivariate analyses did not detect any significant difference between the participating centres.

Discussion

The main finding in our study was that HF outpatients with renal dysfunction and BNP levels in the lower three groups had similar 2-year survival as patients without renal dysfunction and with comparable BNP levels. It has been claimed that BNP and NT-ProBNP lose their predictive value in patients with renal dysfunction [18]. Our data demonstrated that the natriuretic peptides were important predictors of prognosis in outpatients with HF and reduced eGFR and corroborate similar findings in other patient populations [19, 20]. Similar 2-year survival, irrespective of renal function, in patients with BNP/NT-ProBNP levels not in the highest range has not previously been highlighted. Our finding underlines the importance of natriuretic peptides as a prognostic marker also in patients with reduced renal function.

Both BNP and NT-proBNP are inversely related to the GFR [6, 21], and this has been assumed to be an effect of accumulation [6, 18]. BNP is cleared from the circulation through proteolytic cleavage by neutral endopeptidase 24.11 and binding to the clearance receptor natriuretic peptide receptor-C (NPR-C) [22]. In contrast to BNP, NT-ProBNP is not cleared by binding to NPR-C. Both the enzyme and the receptor are highly expressed in the renal tissue, but clearance also takes place in the vascular beds in other organs [7].

Alehagen *et al.* [23] have proposed that elevated NT-ProBNP levels might be an early indication of abnormal cardiac function preceding echocardiographic abnormalities. In asymptomatic patients with CKD not requiring

Table 1. Characteristics of 2076 outpatients with HF: overall and by BNP group, Group 1 had lowest BNP levels, while Group 4 had highest BNP levels[a]

	Valid BNP data *N* = 2076	Count	BNP group 1 (*N* = 381)	BNP group 2 (*N* = 429)	BNP group 3 (*N* = 488)	BNP group 4 (*N* = 778)	P-value for trend
Age (years)	68.5 (12.3)	2076	60.5 (12.5)	66.0 (11.8)	69.5 (11.4)	73.1 (10.7)	<0.001
Male gender	1529 (73.7%)	2076	279 (73.2%)	326 (76.0%)	370 (75.8%)	554 (71.2%)	0.185
BMI (kg/m^2)	26.6 (5.2)	1874	28.4 (5.4)	28.0 (5.5)	26.4 (4.8)	25.0 (4.6)	<0.001
Current smoker	273 (15.7%)	1735	66 (19.9%)	60 (16.7%)	57 (14.5%)	90 (13.9%)	0.081
NYHA class							
I	260 (12.7%)	2051	105 (27.8%)	61 (14.3%)	52 (10.8%)	42 (5.5%)	<0.001
II	961 (46.9%)		200 (52.9%)	241 (56.6%)	258 (53.8%)	262 (34.2%)	
III	805 (39.2%)		73 (19.3%)	123 (28.9%)	167 (34.8%)	442 (57.6%)	
IV	25 (1.2%)		0 (0%)	1 (0.2%)	3 (0.6%)	21 (2.7%)	
Heart rate BPM	70.0 (13.3)	2065	68.7 (11.8)	68.2 (12.7)	69.8 (12.7)	71.6 (14.4)	<0.001
Atrial fibrillation	613 (29.6%)	2068	42 (11.1%)	111 (25.9%)	163 (33.6%)	297 (38.3%)	<0.001
SBP (mmHg)	126.5 (22.1)	2069	128.8 (20.9)	128.2 (20.5)	126.5 (22.6)	124.5 (22.9)	0.004
EF%	34.2 (11.5)	1528	40.4 (11.4)	35.1 (11.2)	34.3 (11.5)	30.4 (10.1)	<0.001
Cause of HF							
IHD	1080 (54.0%)	2001	136 (37.5%)	225 (54.3%)	268 (55.9%)	451 (60.5%)	<0.001
Comorbidities							
Diabetes mellitus	441 (21.4%)	2063	65 (17.2%)	88 (20.7%)	109 (22.5%)	179 (23.1%)	0.121
Hypertension	657 (31.9%)	2062	97 (25.7%)	127 (29.8%)	152 (31.3%)	281 (36.3%)	0.002
COPD	359 (17.4%)	2064	59 (15.6%)	83 (19.5%)	77 (15.8%)	140 (18.1%)	0.353
Cerebrovascular disease	204 (9.9%)	2063	25 (6.6%)	37 (8.7%)	51 (10.5%)	91 (11.8%)	0.037
Claudicatio intermittens	132 (6.4%)	2063	12 (3.4%)	32 (7.5%)	22 (4.5%)	65 (8.4%)	0.002
Vascular disease	316 (15.3%)	2061	36 (9.5%)	66 (15.6%)	70 (14.4%)	144 (18.6%)	0.001
PCI/CABG	871 (42.3%)	2060	118 (31.2%)	184 (43.3%)	223 (46.2%)	346 (44.7%)	<0.001
Medication							
RAAS blockade	1790 (86.5%)	2070	341 (90.0%)	385 (90.2%)	424 (86.9%)	640 (82.5%)	<0.001
ACEi (mg/day)							
0	285 (16.4%)	1738	39 (12.8%)	44 (11.9%)	66 (15.8%)	136 (21.1%)	<0.001
1–10	591 (34.0%)		72 (23.6%)	116 (31.3%)	139 (33.3%)	264 (40.9%)	
>10	862 (49.6%)		194 (63.6%)	211 (56.9%)	212 (50.8%)	245 (38.0%)	
β-Blocker use	1832 (88.4%)	2073	332 (87.4%)	389 (90.7%)	431 (88.5%)	680 (87.5%)	0.369
β-Blocker (mg/day)							
0	242 (11.8%)	2055	48 (12.8%)	40 (9.4%)	56 (11.6%)	98 (12.7%)	0.005
1–100	1266 (61.6%)		204 (54.3%)	265 (62.2%)	297 (61.7%)	500 (64.8%)	
>100	547 (26.6%)		124 (33.0%)	121 (28.4%)	128 (26.6%)	174 (22.5%)	
Diuretics use	1702 (82.0%)	2075	245 (64.5%)	326 (76.0%)	417 (85.5%)	714 (91.8%)	<0.001
Loop diuretics (mg/day)							
0	373 (19.0%)	1966	135 (38.1%)	103 (25.2%)	71 (15.2%)	64 (8.7%)	<0.001
1–40	969 (49.3%)		162 (45.8%)	211 (51.3%)	263 (56.3%)	333 (45.4%)	
>40	624 (31.7%)		57 (16.1%)	97 (23.6%)	133 (28.5%)	337 (45.9%)	
Spironolactone use	467 (22.5%)	2073	73 (19.3%)	92 (21.4%)	104 (21.3%)	198 (25.5%)	0.075
ASA use	1012 (48.8%)	2073	183 (48.3%)	224 (52.2%)	250 (51.2%)	355 (45.7%)	0.102
Statin use	1216 (58.6%)	2074	200 (52.6%)	269 (62.7%)	289 (59.2%)	458 (58.9%)	0.034
CCB use	147 (7.1%)	2073	37 (9.7%)	39 (9.1%)	29 (5.9%)	42 (5.4%)	0.012
Laboratory values							
Haemoglobin g/100 mL	13.8 (1.6)	1989	14.3 (1.4)	14.1 (1.5)	14.0 (1.5)	13.4 (1.6)	<0.001
Se-uric acid mmol/L	455 (130)	1603	407 (109)	434 (117)	450 (121)	495 (130)	<0.001
Se-creatinine mmol/L	106.8 (45.9)	2067	88.7 (26.2)	95.2 (35.1)	101.6 (35.0)	125.4 (56.9)	<0.001
eGFR mL/min	68.4 (25.5)	2067	81.9 (27.7)	75.5 (23.0)	70.0 (22.6)	57.0 (22.5)	<0.001
Se-potassium mmol/L	4.41 (0.46)	2065	4.40 (0.37)	4.40 (0.44)	4.44 (0.46)	4.41 (0.51)	0.573
Se-sodium mmol/L	140.2 (3.0)	2065	140.2 (2.5)	140.3 (2.7)	140.3 (2.9)	140.1 (3.5)	0.536
Se-cholesterol mmol/L	4.67 (1.24)	1508	4.89 (1.31)	4.77 (1.21)	4.68 (1.17)	4.50 (1.24)	<0.001

[a] Data presented as mean (SD) for continuous variables and as count (percentages) for categorical variables. BNP groups were created centre-wise by quartile limits in patients with the eGFR >60 mL/min/1.73 m^2. Patients with the eGFR ≤60 mL/min/1.73 m^2 were then allocated to BNP groups centre-wise due to their level of natriuretic peptides.

ACEi mg/day, daily enalapril equivalent dose; ASA, acetylsalicylic acid; β-blocker mg/day, daily metoprolol equivalent dose; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; loop diuretic mg/day, daily furosemide equivalent dose; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention and/or coronary artery bypass graft; RAAS blockade, use of angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker; SBP, systolic blood pressure; Se-, serum; vascular disease, earlier stroke and/or peripheral vascular disease.

dialysis, increased levels of BNP/NT-ProBNP are predictive of depressed left ventricular ejection fraction, increased left ventricular mass and coronary and peripheral vascular disease [10, 11]. Thereby, elevated levels of natriuretic peptides in CKD patients could reflect increased production as patients with CKD are at high risk of cardiovascular diseases [8, 14, 24, 25].

We observed an exponentially increasing hazard of all-cause mortality by time in patients with renal dysfunction and initially relatively low BNP levels. Lower levels of natriuretic peptides predicted a favourable prognosis irrespective of renal function during the first years of follow-up. However, in patients with renal dysfunction and initially lower levels of BNP/NT-ProBNP, the hazard of all-cause mortality increased steeply with time. Beyond 3 years of follow-up, the hazard of all-cause mortality was much higher in patients with renal dysfunction than in patients with preserved eGFRs, and interestingly independent of the level of natriuretic peptides at the start of follow-up. This finding may provide insights into the increased susceptibility to progressive heart and cardiovascular diseases in patients with CKD [8, 9, 26, 27]. Thus, our data indicate that in patients with HF and renal dysfunction, lower levels of BNP/NT-ProBNP may predict

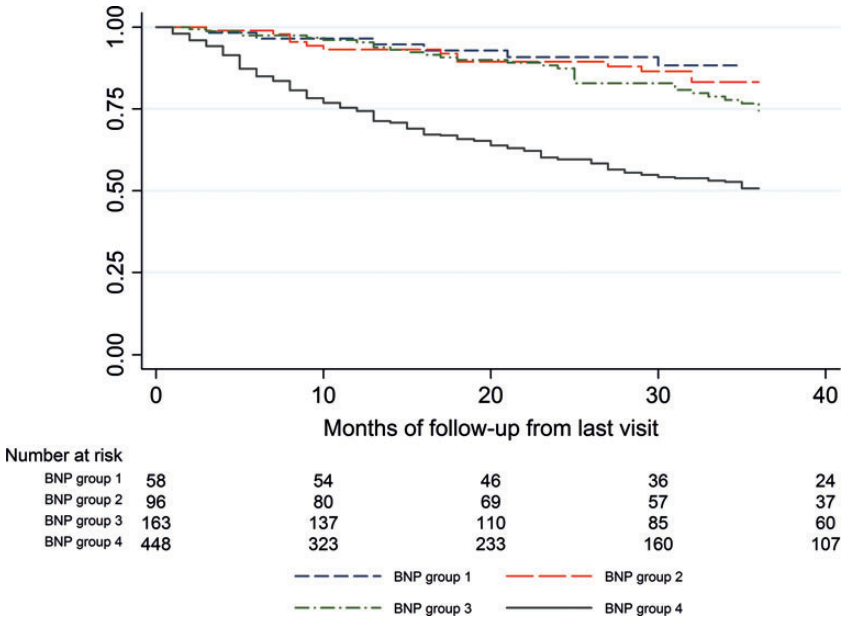

Fig. 2. Survival classified by BNP groups in 775 outpatients with HF and renal dysfunction. Kaplan–Meier survival plot comparing patient survival in the different BNP groups in patients with an eGFR ≤60 mL/min/1.73 m^2. BNP group 1 had lowest levels of natriuretic peptides, while BNP group 4 presented the highest levels. BNP = B-type natriuretic peptide, eGFR = estimated glomerular filtration rate.

favourable short-term prognosis, but within years the negative effect of reduced eGFR will exacerbate the prognosis substantially.

NT-proBNP > 2180 pg/mL and for BNP > 504 pg/mL were the average cut-off values for the highest BNP group among the participating centres. Various cut-off limits have been proposed when the risk of morbidity and mortality increases in patients with chronic HF [1, 19, 25, 28]. In our study, patients with an eGFR ≤60 mL/min/1.73 m^2, and BNP levels in the lower three groups (i.e. NT-ProBNP < 2180 pg/mL or BNP < 504 pg/mL) had similar 3-year all-cause mortality despite large differences in BNP values. The number of renal patients within the two lowest BNP groups was low, and a type II error cannot be excluded as explanation for why we could not find any difference in all-cause mortality among the three lower BNP groups. However, as the increase in plasma concentration of the natriuretic peptides is exponential as the wall tension increases, only a minor difference in mortality between quartiles 1–3 of natriuretic peptides in HF patients has been reported by others earlier [3].

Our study had some other important strengths and limitations. Follow-up was long and the study population was large and representative of outpatients with HF as all patients admitted to the participating HF clinics and met the diagnostic criteria of HF were included. Although the number of patients was high, the subgroup analyses may have been underpowered. Given the observational study design, no conclusions on the reason for the strong correlation between renal function and levels of BNP/NT-ProBNP could be made. However, as the BNP levels predicted 2-year survival similarly irrespective of renal function, our results may suggest that the BNP/NT-ProBNP level could be interpreted as an indicator of the burden of cardiovascular disease at the time of the blood sampling rather than an effect of renal function.

Natriuretic peptides were analysed using various methods at the different hospitals and different assays are not necessarily comparable even when analysing the same peptide [16]. In order to correct for different reference values and methods, and to increase power to the statistical analyses, the patients were allocated to BNP groups centre-wise based upon quartile levels in patients without renal dysfunction, assuming that the populations at each centre were comparable. Entering treatment centre as an independent categorical variable in the different multivariate analyses did not affect our results, and the treatment centre was not an independent predictor of all-cause mortality. This indicates that the assumption of comparable populations at the different centres was met.

It might be criticized that BNP and NT-ProBNP were pooled together as the mechanisms of degradation differ between the two peptides and the correlation with the eGFR is found to be different for the two peptides [6, 11]. Elevation of NT-ProBNP is claimed to be more accentuated in elderly patients and in those with renal disease as the clearance is thought to be more kidney dependent [29]. Van Kimmenade *et al*. [5] recently found BNP and NT-proBNP to be equally dependent on renal function for their clearance in a mechanistic study [5]. Furthermore, both the peptides are found to be similarly useful prognostic tools in renal patients [2, 25]. We found no interaction between BNP and NT-ProBNP in the Cox models. Therefore, we assumed that centre-wise allocation to BNP groups would provide similar information irrespective of whether BNP or NT-ProBNP were used at the different centres. However, we cannot exclude the possibility that difference may exist between which peptide analysed and assay used.

Analyses were restricted to existing data in the Norwegian Heart Failure Registry. As a consequence, we were not able to evaluate the full spectrum of CKD. Renal dysfunction was defined as eGFR ≤ 60 mL/min/1.73 m^2 and renal function was treated as a dichotomized variable. There were few patients with GFRs <30 mL/min/1.73 m^2

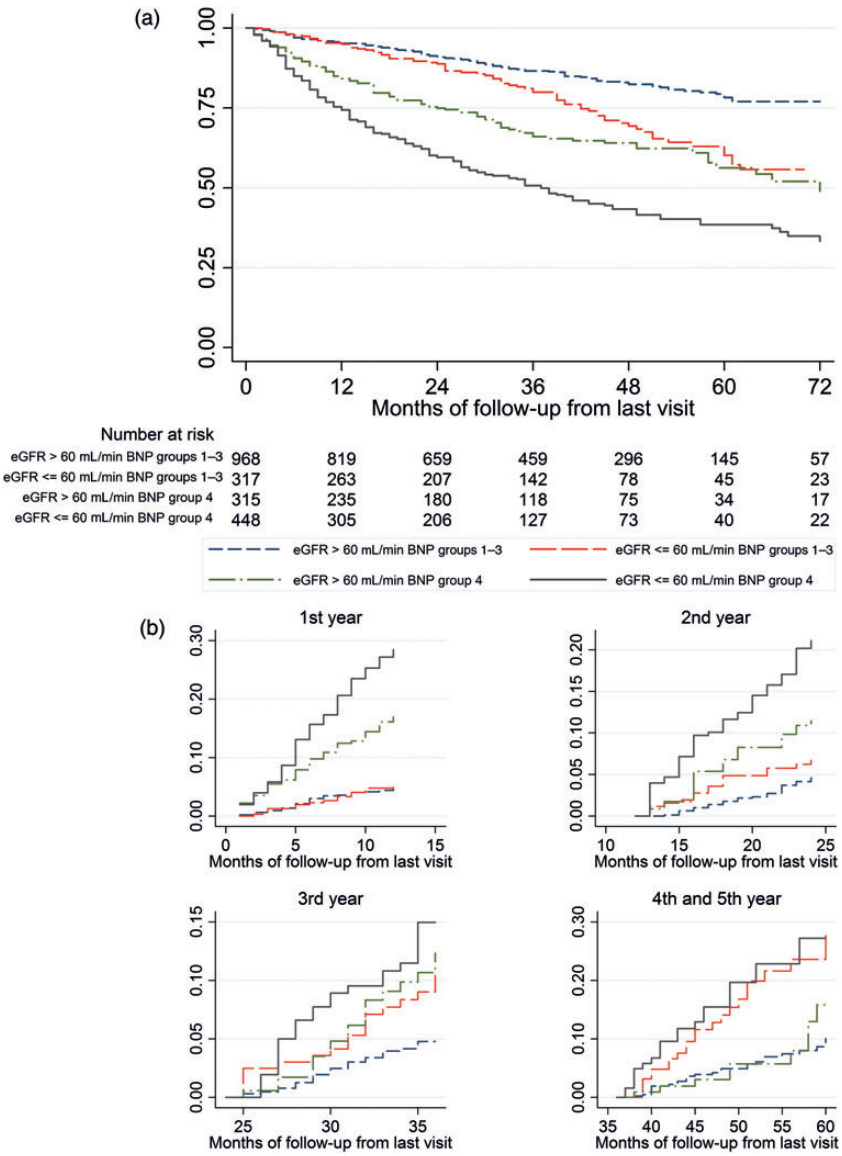

Fig. 3. Survival and time interval all-cause mortality hazard plots classified by renal function and BNP group in 2076 outpatients with HF. Kaplan–Meier survival plot comparing the groups of renal function and the level of natriuretic peptides. The EGFRs above or below 60 mL/min/1.73 m^2 were combined with BNP levels in or below BNP group 4, which contained the patients with the highest BNP levels (**a**). Time interval Nelson–Aalen hazard plots demonstrating increasing hazard of all-cause mortality by time in patients with renal dysfunction and BNP groups 1–3, during first year, second year, third year and fourth and fifth year of follow-up (**b**). eGFR = estimated glomerular filtration rate, BNP = B-type natriuretic peptide.

Table 2. Cox regression all-cause mortality analyses comparing combined groups of eGFRs above or below 60 mL/min/1.73 m^2 and BNP in the highest group or below[a]

	Crude HR	95% CI	*P*	Adj HR[b]	95% CI	*P*	Multiple adj HR[c]	95% CI	*P*
First 2 years									
eGFR > 60 mL/min and BNP 1–3	1			1					
eGFR ≤ 60 mL/min and BNP 1–3	1.25	0.82–1.89	0.302	0.99	0.65–1.53	0.991	0.85	0.54–1.33	0.467
eGFR > 60 mL/min and BNP 4	3.11	2.25–4.28	<0.001	2.60	1.87–3.60	<0.001	2.07	1.46–2.93	<0.001
eGFR ≤ 60 mL/min and BNP 4	5.38	4.11–7.04	<0.001	3.96	2.96–5.29	<0.001	2.76	2.02–3.77	<0.001
Beyond second year									
eGFR > 60 mL/min and BNP 1–3	1			1					
eGFR ≤ 60 mL/min and BNP 1–3	2.66	1.81–3.90	<0.001	1.88	1.26–2.80	0.002	1.97	1.27–3.07	0.003
eGFR > 60 mL/min and BNP 4	1.98	1.28–3.08	0.002	1.53	0.98–2.40	0.061	1.50	0.91–2.45	0.109
eGFR ≤ 60 mL/min and BNP 4	3.48	2.41–5.01	<0.001	2.17	1.47–3.21	<0.001	2.15	1.40–3.31	<0.001

[a]Adj, adjusted; BNP 1–3, B-type natriuretic peptide groups 1, 2 or 3; BNP 4, B-type natriuretic peptide group 4; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio.
[b]Adjusted for age and gender.
[c]Multivariate adjusted for age, New York Heart Association function class, ischaemic heart disease, history of hypertension and atrial fibrillation.

in our study, and the results should be interpreted with caution in patients with severe renal dysfunction.

Only 33% of the patients in the registry had valid BNP registrations and could be included in the study. Patients included in the early years of the registry were less likely to have valid BNP/NT-ProBNP registrations. Furthermore, several centres had changed their assays during the study and small centres were not included as they did not meet the criteria of 40 patients analysed by the same assay. Other reasons for missing BNP values in patients may exist and thus, selection bias cannot be excluded.

In summary, natriuretic peptides provided important prognostic information on outpatients with HF and renal dysfunction. Heart failure patients with BNP/NT-ProBNP levels in the lower three BNP groups had a similar 2-year prognosis irrespective of renal function. Our findings lend support to the opinion that BNP levels may be interpreted as the current burden of cardiovascular disease also in patients with renal dysfunction, and should not be interpreted only as a result of accumulation. Furthermore, patients with renal dysfunction had increased risk of all-cause mortality beyond 2 years of follow-up regardless of the level of natriuretic peptides at baseline. This could mirror more rapid progression of cardiovascular disease in patients with CKD. To assess both natriuretic peptides and GFRs in patients with HF may prove valuable in the evaluation of short- and long-term prognosis and in the guidance of treatment. However, prospective trials are needed to answer that question.

Conflict of interest statement. T.O. has received speaker honoraria from Roche Diagnostics, Siemens Healthcare Diagnostics and Abbott Diagnostics. Akershus University Hospital has received research support from Roche Diagnostics and Abbott Diagnostics.

Reference

1. Richards AM, Doughty R, Nicholls MG *et al*. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia–New Zealand Heart Failure Group. *J Am Coll Cardiol* 2001; 37: 1781–1787
2. Masson S, Latini R, Anand IS *et al*. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem* 2006; 52: 1528–1538
3. Alehagen U, Lindstedt G, Levin LA *et al*. Risk of cardiovascular death in elderly patients with possible heart failure. B-type natriuretic peptide (BNP) and the aminoterminal fragment of ProBNP (N-terminal proBNP) as prognostic indicators in a 6-year follow-up of a primary care population. *Int J Cardiol* 2005; 100: 125–133
4. Dhar S, Pressman GS, Subramanian S *et al*. Natriuretic peptides and heart failure in the patient with chronic kidney disease: a review of current evidence. *Postgrad Med J* 2009; 85: 299–302
5. van Kimmenade RR, Januzzi JL Jr., Bakker JA *et al*. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. *J Am Coll Cardiol* 2009; 53: 884–890
6. McCullough PA, Duc P, Omland T *et al*. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the breathing not properly multinational study. *Am J Kidney Dis* 2003; 41: 571–579
7. Martinez-Rumayor A, Richards AM, Burnett JC *et al*. Biology of the natriuretic peptides. *Am J Cardiol* 2008; 101: 3–8
8. Ronco C, Haapio M, House AA *et al*. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; 52: 1527–1539
9. Astor BC, Hallan SI, Miller ER III *et al*. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol* 2008; 167: 1226–1234
10. DeFilippi CR, Fink JC, Nass CM *et al*. N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. *Am J Kidney Dis* 2005; 46: 35–44
11. Vickery S, Price CP, John RI *et al*. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 2005; 46: 610–620
12. de Silva R, Nikitin NP, Witte KK *et al*. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. *Eur Heart J* 2006; 27: 569–581
13. Waldum B, Westheim AS, Sandvik L *et al*. Renal function in outpatients with chronic heart failure. *J Card Fail* 2010; 16: 374–380
14. McAlister FA, Ezekowitz J, Tonelli M *et al*. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; 109: 1004–1009
15. Grundtvig M, Gullestad L, Hole T *et al*. Characteristics, implementation of evidence-based management and outcome in patients with chronic heart failure results from the Norwegian heart failure registry. *Eur J Cardiovasc Nurs* 2011; 10: 1044–49
16. Yandle T, Fisher S, Espiner E *et al*. Validating aminoterminal BNP assays: a word of caution. *Lancet* 1999; 353: 1068–1069
17. Katz MH. *Assumptions of multiple linear regression, multiple logistic regression, and propotional hazards analysis*. *Multivariable Analysis.* Cambridge, UK: Cambridge University Press, 2006; 38–67
18. Luchner A, Hengstenberg C, Lowel H *et al*. Effect of compensated renal dysfunction on approved heart failure markers: direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP. *Hypertension* 2005; 46: 118–123
19. Gardner RS, Chong KS, O'Meara E *et al*. Renal dysfunction, as measured by the modification of diet in renal disease equations, and outcome in patients with advanced heart failure. *Eur Heart J* 2007; 28: 3027–3033
20. van Kimmenade RR, Januzzi JL Jr., Baggish AL *et al*. Amino-terminal pro-brain natriuretic Peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction? *J Am Coll Cardiol* 2006; 48: 1621–1627
21. Richards M, Nicholls MG, Espiner EA *et al*. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. *J Am Coll Cardiol* 2006; 47: 52–60
22. McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. *Trends Endocrinol Metab* 2005; 16: 469–477
23. Alehagen U, Lindstedt G, Eriksson H *et al*. Utility of the amino-terminal fragment of pro-brain natriuretic peptide in plasma for the evaluation of cardiac dysfunction in elderly patients in primary health care. *Clin Chem* 2003; 49: 1337–1346
24. Takami Y, Horio T, Iwashima Y *et al*. Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. *Am J Kidney Dis* 2004; 44: 420–428

25. Austin WJ, Bhalla V, Hernandez-Arce I *et al*. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *Am J Clin Pathol* 2006; 126: 506–512
26. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. *Semin Dial* 2003; 16: 101–105
27. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305
28. Palazzuoli A, Gallotta M, Quatrini I *et al*. Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure. *Vasc Health Risk Manag* 2010; 6: 411–418
29. McCullough PA, Neyou A. Comprehensive review of the relative clinical utility of B-type natriuretic peptide and N-terminal Pro-B-type natriuretic peptide assays in cardiovascular disease. *Open Heart Fail J* 2009; 2: 6–17

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